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4-(4-trans-hydroxycyclohexyl)amino-2-phenyl-7h-pyrrolo [2, 3d]pyrimidine hydrogen mesylate
and its polymorphic forms
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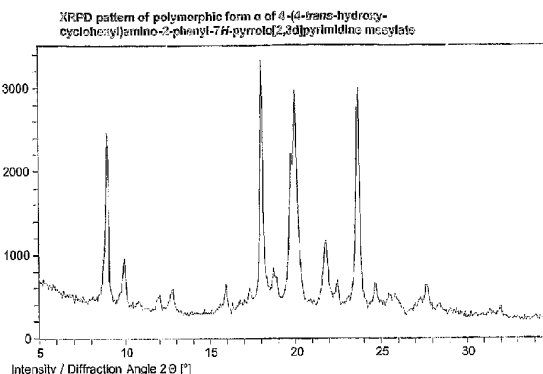
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(54) Title: 4-(4-TRANS-HYDROXYCYCLOHEXYL)AMINO-2-PHENYL-7H-PYRROLO[2,3-D]PYRIMIDINE HYDROGEN
MESYLATE AND ITS POLYMORPHIC FORMS



(57) Abstract: The present invention relates to the novel compound 4-(4-trans-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine hydrogen mesylate, the polymorphic α and β forms thereof and a method for the production of said compounds.

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4-(4-TRANS-HYDROXYCYCLOHEXYL)AMINO-2-PHENYL-7H-PYRROLO' 2, 3D!

PYRIMIDINE HYDROGEN MESYLATE AND ITS POLYMORPHIC FORMS

5 The present invention relates to the novel compound 4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate, different polymorphic forms thereof and a method for the production of said compounds.

10 4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine is disclosed in WO 99/62518 (compound 18 on page 53) and is a selective Adenosine-1 Receptor agonist that may be used in the treatment of essential hypertension, congestive heart failure and renal failure.

15 During further development of said compound in the mentioned indications, it appeared that the compound as disclosed in WO 99/62518 has the serious drawback of a low solubility in gastrointestinal fluids.

The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

25 Throughout the description and claims of the specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

30 It is an aspect of the present invention to provide a salt of 4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine that is a crystalline, homogeneous and stable product and that has superior solubility properties.

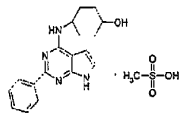
This aspect can be achieved, according to the present invention by the hydrogen mesylate salt of 4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine. In the framework of the present application this compound is further

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referred to as 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]-pyrimidine mesylate. The compound has the following structure:

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In contrast to the camphorsulfonate, mono-ethanesulfonate, mono-isethionate, phosphate and sulfate salts the mesylate salt is highly soluble in water. Further 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]-pyrimidine mesylate appears to be very stable at ambient conditions.

Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine mesylate was found to exist in two polymorphic forms, further indicated as polymorphic forms α and β . Both polymorphic forms have improved solubility, although form α has a better solubility than form β . Form α is metastable with respect to form β . Form β is the currently known stable form.

Substantially pure form α can be obtained in a laboratory setting by adding a solution of methane sulfonic acid in methanol to a suspension of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine in methanol, followed by the addition of isopropanol. Substantially pure form β can be obtained by adding a solution of methane sulfonic acid in ethanol to a solution of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine in ethanol, followed by the addition of water and stirring. The pure form β can also be obtained by stirring samples of pure form α in a mixture of ethanol and water.

The term substantially pure means a purity of at least 90%, preferably at least 95%, even more preferred 97% and most preferred at least 99%.

The polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine mesylate according to the present invention is defined by the following physicochemical characteristics:

- (i) An X-ray powder diffraction (=XRPD) pattern having characteristic reflexes (expressed in degrees of diffraction angle 2θ) at: 9.0, 10.0, 12.8, 15.9, 18.1, 18.8, 19.8, 20.1, 21.8, 23.7. Diffraction angles are indicated as mean values ($\pm 0.1^\circ$) of six independent measurements. The complete XRPD pattern for the polymorphic form α is shown in Figure 1.
- (ii) An infrared (=IR) spectrum recorded in attenuated total reflectance (=ATR) having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3248, 1644, 1455, 1381, 1368, 1292, 1117, 1092, 1042, 743. The complete IR spectrum for the polymorphic form α is shown in Figure 2.
- (iii) A melting point at approximately 248 °C (onset temperature) measured by DSC. The complete DSC trace for the polymorphic form α is shown in Figure 3.

The polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine mesylate according to the present invention is defined by the following physicochemical characteristics:

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- (i) An X-ray powder diffraction (=XRPD) pattern having characteristic reflexes (expressed in degrees of diffraction angle 2θ) at: 9.3, 11.8, 12.2, 17.6, 18.0, 18.6, 19.3, 20.8, 23.4, 26.5. Diffraction angles are indicated as mean values ($\pm 0.1^\circ$) of four independent measurements. The complete XRPD pattern for the polymorphic form β is shown in Figure 4.
- (ii) An infrared (=IR) spectrum recorded in attenuated total reflectance (=ATR) having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3338, 3279, 1602, 1564, 1389, 1219, 1154, 1134, 1034, 732. The complete IR spectrum for the polymorphic form β is shown in Figure 5.
- (iii) A melting point at approximately 220 °C (onset temperature) measured by DSC. The complete DSC trace for the polymorphic form β is shown in Figure 6.

4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine is known to be useful in treating and/or preventing essential hypertension, congestive heart failure and renal failure in mammals. 4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine can also be administered as its hydrogen mesylate. It is effective over a wide dosage range. The term "therapeutically effective amount" in the framework of the present invention refers to an amount capable of diminishing the adverse symptoms of a particular disease in a subject. With a "subject" is meant a human subject of either sex and of any age, but also any non-human animal, particularly a domestic or companion animal (such as a cat, dog, monkey, cow or horse). Preferred dosage is in the range of from about 0.01 to about 200 mg body weight per day. In the treatment of adult humans range of about 0.1 to about 100 mg in single or divided doses is particularly preferred. The particular dose of compound administered according to the present invention will, however, be determined by the particular circumstances surrounding the case, including the weight, the age, the severity of the symptoms and the individual response of the patient and will also depend on the route of administration. Therefore the above mentioned dosage range are not intended to limit the scope of the present invention in any way.

4-(4-*trans*-hydroxycyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine mesylate may be administered in different ways, e.g orally, transdermally and/or parenterally. In the case of acute heart failure the compound is preferably administered parenterally. Compositions intended for oral, transdermal and/or parenteral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions. Such compositions may comprise one or more materials selected from the group consisting of coloring agents, flavoring agents,

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sweetening agents and preservatives. Formulations for oral use may be tablets which may contain the active ingredient in admixture with pharmaceutically acceptable excipients, such as binding agents (e.g. starch, acacia, gelatin), lubricating agents (e.g. stearic acid, magnesium stearate, talc), granulating and disintegrating agents (e.g. corn starch, alginic acid) and inert diluents (e.g. calcium phosphate, sodium phosphate, calcium carbonate, sodium carbonate, lactose). Formulations for oral use may also be soft gelatin capsules wherein the active ingredient is mixed with water or an oily medium such as liquid paraffin, peanut oil, or olive oil or hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent such as kaolin, calcium carbonate or calcium phosphate.

The following examples are only intended to further illustrate the invention, in more detail, and therefore these examples are not deemed to restrict the scope of the invention in any way.

Example 1. Preparation of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate.

701 g of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine prepared according to the method described in WO 99/62518 are suspended in 4.5 L methanol. a solution of 240 g methane sulfonic acid in 750 mL methanol is added under stirring, leading to a clear solution. The mixture is concentrated to 1900 g, then 5.5 L isopropanol are added at room temperature and the mixture is stirred for 44 h. The product is filtered, washed four times with 0.5 L isopropanol, each and dried for 40 h at 95 °C in a vacuum drying oven to give 780 g of the title compound as crystalline modification α .

Example 2. Preparation of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate.

2.00 g of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine (= 6.50 mmol) was dissolved in 70 ml of acetone at reflux temperature. Under stirring at reflux temperature there was added a solution of 0.62 g of methanesulfonic acid (= 6.50 mmol) in 7 ml of acetone. The reaction mixture was stirred at reflux temperature for 10 minutes. After this the reaction mixture was cooled to room temperature by removing the heating mantle. The resulting suspension was stirred for 1 hour at 2 °C. The product was collected by filtration, washed twice with 5 ml of acetone and dried

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under vacuo at 50 °C for 24 hours. This gave 2.49 g of crystalline modification α (= 95 % c/c).

The polymorphic form α was also obtained from the solvents acetonitrile and 2-butanone, according to a similar procedure.

Example 3. Preparation of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate.

10 2.00 g of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine (= 6.50 mmol) was dissolved in a mixture of 45 ml of acetone and 5 ml of water at reflux temperature. Under stirring at reflux temperature there was added a solution of 0.62 g of methanesulfonic acid (= 6.50 mmol) in 5 ml of acetone. The reaction mixture was stirred at reflux temperature for 10 minutes. After this the reaction mixture was cooled to room temperature by removing the heating mantle. The resulting suspension was stirred for 45 hours at room temperature. The product was collected by filtration, washed twice with 5 ml of acetone and dried under vacuo at 50 °C for 24 hours. This gave 2.26 g of crystalline modification β (= 86 %).

20 The polymorphic form β was also obtained from the solvent mixtures acetonitrile/water and 2-butanone/water, according to a similar procedure.

Example 4. Rearrangement of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate into its polymorphic form β .

5302 g of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate modification α was stirred in 20 l of ethanol and 2 L of water for 5 days at ambient temperature. The product was filtrated and dried at 70 °C for 40 h in a circulating air drier to give 3444 g of the title compound as crystalline modification β .

Example 5. Analytical methods.

XRPD patterns were measured on a diffractometer using monochromatic CuK α radiation (tube voltage 40 kV, tube current 40 mA). IR spectra were recorded on a Fourier transform IR spectrometer in attenuated total reflectance (silicon crystal) with a spectral resolution of 2 cm⁻¹ using a deuterated triglycine sulfate detector.

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Melting points were determined on a DSC apparatus as onset temperatures of the melting endotherm using 40 μ L aluminum crucibles with a pierced lid. Temperature program: heating from 25 °C up to 300 °C with 10 K min⁻¹. N₂ atmosphere at a flow of 60 mL min⁻¹.

- 5 Solubility measurements were carried out with the shake flask method according to the OECD guideline at 25°C (OECD Guideline for testing of chemicals, No. 105 (issued 12 May 1981)).

10 **Example 6. Solubility of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine and its mesylates polymorphic form α and β .**

Measurement of the solubility of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine and its mesylates polymorphic form α and β in purified water gave the following results

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Compound	Solubility in mg/l
Base	0.0058
Polymorph α	77
Polymorph β	18.5

Claims

1. 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate.
2. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α) exhibiting an X-ray powder diffraction (=XRPD) pattern having characteristic reflexes (expressed in degrees of diffraction angle 2θ) at: 9.0, 10.0, 12.8, 15.9, 18.1, 18.8, 19.8, 20.1, 21.8, 23.7.
3. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), characterized by an X-ray powder diffraction (=XRPD) pattern shown in Figure 1..
4. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), exhibiting an infrared (=IR) spectrum recorded in attenuated total reflectance (=ATR) having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3246, 1644, 1455, 1381, 1368, 1292, 1117, 1092, 1042, 743.
5. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), characterized by a complete IR spectrum shown in Figure 2.
6. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), exhibiting an melting point at approximately 248 °C.
7. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (α), characterized by a complete DSC trace shown in Figure 3.
8. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β), exhibiting an X-ray powder diffraction (=XRPD) pattern having characteristic

reflexes (expressed in degrees of diffraction angle 2θ) at: 9.3, 11.6, 12.2, 17.6, 18.0, 18.6, 19.3, 20.6, 23.4, 26.5.

9. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,6*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β),
5 characterized by an X-ray powder diffraction (=XRPD) pattern shown in in Figure 4.
10. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β),
10 exhibiting an infrared (=IR) spectrum recorded in attenuated total reflectance (=ATR) having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3338, 3279, 1602, 1564, 1389, 1219, 1154, 1134, 1034, 732.
11. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β),
15 characterized by a complete IR spectrum shown in in Figure 5.
12. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β),
20 exhibiting an melting point at approximately 220 °C.
13. Crystalline 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1, in a polymorphic form (β),
25 characterized by a complete DSC trace shown in in Figure 6.
14. A pharmaceutical composition comprising an effective amount of the compound according to any one of claims 1 to 13.
30
15. A pharmaceutical composition according to claim 14, intended for parenteral use.
16. A compound as claimed in any one of claims 1 to 13 for use in medicine.

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17. Use of the compound according to any one of claims 1 to 13 for the preparation of a medicament for the treatment of essential hypertension, congestive heart failure and renal failure.
- 5 18. A method of treating essential hypertension, congestive heart failure and renal failure comprising the administration to a subject in need thereof of a compound of any one of claims 1 to 13.
- 10 19. 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3*d*]pyrimidine hydrogen mesylate according to claim 1 substantially as hereinbefore described with reference to any one of the Examples or Figures.

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PHILLIPS ORMONDE & FITZPATRICK

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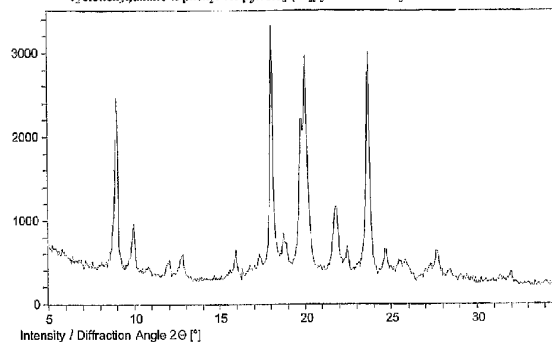
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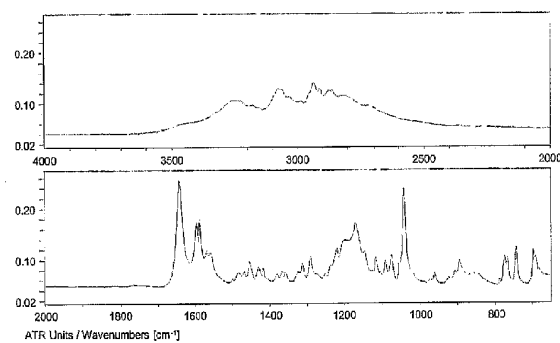
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Figure 1: XRPD pattern of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate

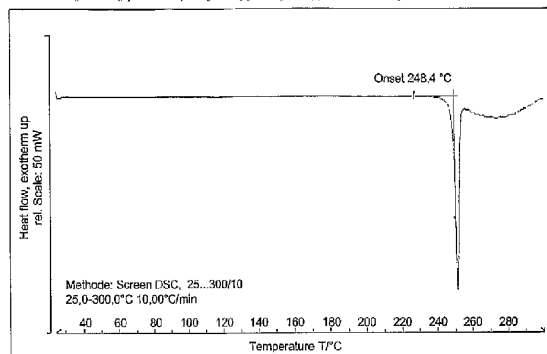


5 Figure 2: IR (ATR) spectrum of form polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate



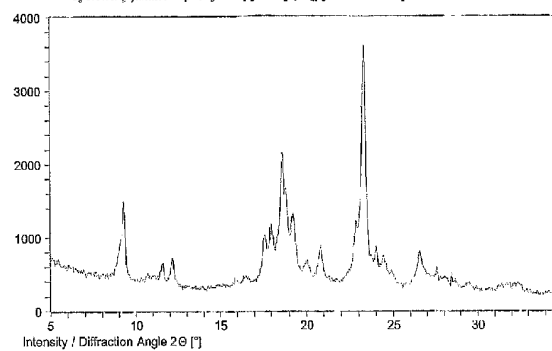
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Figure 3: DSC trace of form polymorphic form a of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine mesylate

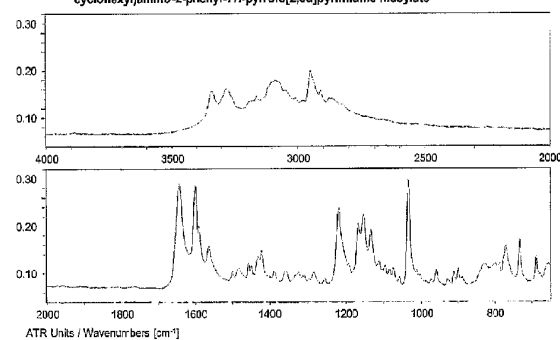


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Figure 4 XRD pattern of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine mesylate



5 Figure 5 IR (ATR) spectrum of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine mesylate



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Figure 8: DSC trace of polymorphic form β of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine mesylate

